

**Nasal High Frequency Oscillation Ventilation(NHFOV) vs.
Nasal Continuous Positive Airway Pressure(NCPAP) vs
Nasal Intermittent Positive Pressure Ventilation (NIPPV)
as Post-extubation Respiratory Support in Preterm Infants
With Respiratory Distress Syndrome:a Multicenter
Randomized Controlled Trial**

(NCT03181958)

2 September 2021

Informed Consent

Dear Madam or Sir

We are considering inviting you and your baby to participate in a multicenter, randomized, controlled study: Continuous positive airway pressure (CPAP) vs noninvasive positive pressure ventilation (NIPPV) vs noninvasive high frequency oscillation ventilation (NHFOV) as post-extubation support in preterm neonates which is a scientific research project funded by Scientific Research Projects unit of Chongqing (Project- cstc2016shms-ztx13001). The trial has been approved by the Ethical Committee of the Third Affiliated Hospital of Third Military Medical University-Human Research Protection Program (with the n.201721).

Before you decide whether to participate in this study, please read the following as carefully as possible. It can help you understand the procedure, duration, benefits, risks and discomfort of this study. If you wish, you can also discuss it with your relatives or friends, or ask your doctor for an explanation to help you make a decision.

Background

Clinical trials have shown that a relevant proportion of preterm neonates eventually need invasive mechanical ventilation (IMV) during their hospitalization. Prolonged duration of IMV is a well known risk factor for the development of bronchopulmonary dysplasia (BPD), early death, later neurologic impairment and rehospitalization during the first year of life in the preterm infants. Owing to the collapsing chest wall and poor diaphragmatic strength, neonates born very preterm at ≤ 32 weeks of gestational age have a high risk of extubation failure. To minimize the duration of IMV, various of noninvasive ventilation (NIV) modes are available to reduce the risk of extubation failure in neonatal intensive units (NICUs). Nasal continuous positive airway pressure (NCPAP) was the first successful NIV mode to facilitate the transition to spontaneous breathing following extubation. However, the rate of extubation failure while receiving NCPAP in very preterm infants was about 25 to 50%. Nasal intermittent positive pressure ventilation (NIPPV) is

another type of NIV that uses a ventilator to deliver intermittent peak pressure during NCPAP to provide respiratory support. The systematic review has shown NIPPV reduces the rate of extubation failure more effectively than NCPAP but no significant reduction in rate of chronic lung disease. In addition, the main drawback of neonatal NIPPV is the lack of synchronization, which is difficult to achieve and is often unavailable. Noninvasive high frequency oscillatory ventilation (NHFOV) is a newer modality for NIV that consists on the application of a bias flow generating a continuous distending pressure with oscillations superimposed on spontaneous tidal breathing. NHFOV may be beneficial because it allows to increase mean airway pressure (Paw) avoiding gas trapping and hypercarbia, thanks to the superimposed high frequency oscillations. NHFOV also provides the advantages of invasive high frequency oscillatory ventilation (no need for synchronization, high efficiency in CO₂ removal, less volume/barotrauma) and nasal CPAP (noninvasive interface, oxygenation improvement by the increase in functional residual capacity through alveolar recruitment). Recently, NHFOV has gained popularity for use in NICU.

Objectives

We conducted this multicenter, randomized trial to test the hypothesis that NHFOV is more efficacious than NCPAP or NIPPV to reduce the need for IMV in neonates born between 25 and 32 weeks' gestation, after their first extubation and until their final NICU discharge.

Which ones are not suitable to participate in the study?

1. major congenital anomalies or chromosomal abnormalities
2. neuromuscular diseases
3. upper respiratory tract abnormalities
4. need for surgery known before the first extubation

5. Grade IV-intraventricular hemorrhage (IVH) occurring before the first extubation
6. birth weight <600 g
7. suspected congenital lung diseases or malformations or pulmonary hypoplasia.

Which ones are needed for this study?

1. gestational age (GA) between 25⁺⁰ and 32⁺⁶ weeks
2. assisted with any type of endotracheal ventilation
3. post-conceptional age <36 weeks
4. ready to be extubated for the first time (extubation readiness requires fulfilling of all the following criteria: **a.** having received at least one loading dose of 20 mg/kg and 5 mg/kg daily maintenance dose of caffeine citrate; **b.** pH>7.20 and PaCO₂≤60 mmHg; **c.** Paw of 7-8 or 8-9 cmH₂O, in conventional and oscillatory ventilation, respectively; **d.** FiO₂≤0.30; **e.** sufficient spontaneous breathing effort, as per clinical evaluation)
5. Willingness to participate in this clinical trial and signing the consent form.

What would I do to participate in this study?

Before your baby is enrolled in the study, your doctor will record your baby medical history to determine if your baby is eligible to participate in this study. If your baby meet the inclusion criteria through screening, the study will be conducted as follows:

1. Your baby will be given a random number generated by computer will determine your baby grouping. Neither you nor your doctor can know or choose the treatment in advance. All three noninvasive ventilation modes are safe and effective. Twins will be allocated in the same treatment group. Infants randomized to one arm cannot crossover to the other or vice-versa during the study. Patients will remain under the assigned respiratory support until the weaning criteria will be met. In case of intubation, when the baby will be extubated, he will receive again his original treatment according to randomization
2. In the trial, PaCO₂ will be measured using arterialized capillary blood gas analysis and/or

transcutaneous monitoring according to local policies. Transcutaneous monitoring will be performed according to the American Association of Respiratory Care guidelines and the manufacturer's recommendations. Frequency of blood gas analysis will be decided by the attending clinicians. All neonates will be continuously monitored for SpO₂, ECG, heart and respiratory rate. To avoid abdominal distention, a feeding tube will be placed in the stomach through the mouth and gas will be periodically aspirated according to nurses' evaluation in all study arms.

3. The study intervention (CPAP, NIPPV or NHFOV) will be stopped when the above-described minimum parameters are reached and maintained for at least 48h with the following: **(1)** FiO₂≤0.25; **(2)** Silverman score <3; **(3)** no apneas or bradycardia without spontaneous recovery. If a baby will desaturate (SpO₂<85% with FiO₂>25%) or has relevant dyspnea (Silverman≥3) or more than 3 apneas/d, the intervention (CPAP, NIPPV or NHFOV) will be restarted for at least 48h and then re-evaluated.

The benefits, risks, and costs associated with participating in this study

Benefits and costs

If you participate in this study, you will receive standardized and specialized treatment for better outcomes. During treatment, you will receive free ventilator treatment after enrollment. However, Other treatment costs need to be paid for by yourself.

Adverse events

During the process of trial, if your baby is allocated in the CPAP group, your baby may have a high risk of extubation failure. Conversely, if your baby is allocated in the NIPPV group or NHFOV group, Some adverse reactions such as abdominal distention or air leakage may occur. The corresponding treatment of adverse reactions during CPAP, NIPPV or NHFOV is free of charge.

Doctors will do their best to prevent and treat any injuries that may result from this study. If an adverse event occurs in the clinical trial, the medical expert committee will determine whether it is related to the trial process. The sponsor will provide economic compensation for the damage related to the trial with reference to the provisions of the Quality Management Standard for Drug Clinical Trials of China. If you experience any indisposition during the study, your doctor will make a judgment and give you appropriate treatment.

Is my personal information confidential?

All your medical records will be kept at the hospital where you are attending. Researchers and

ethics committees will be allowed access to your medical records. Your identity will not be disclosed in any public report of the results of this study. We will make every effort to protect your privacy within the scope of the law.

How can I get more information?

You can ask any questions about this study at any time and get answers accordingly. If, during the course of the study, there is any significant new information that may affect your willingness to continue to participate in the study, your doctor will keep you informed.

Do I have the right to participate in or withdraw from the study voluntarily?

Participation in the study is entirely up to you. You may refuse to participate in or withdraw from the study at any time without affecting your relationship with your physician. Your continued participation in this study may be discontinued at any time by the physician or the investigator for your best interest./// You may also be required to undergo a laboratory and medical examination if your doctor deems it necessary. After exiting the trial, you may continue to receive standardized treatment, depending on your condition.

What should I do now?

It is up to you and your family to decide whether to participate in this study. Before you make the decision to participate in the study, ask your doctor as many questions as you can about the trial. If you decide to participate in this study, please let your doctor know and he will arrange all the staff for you. Thank you for reading the above material. Please keep this information.

Statement of Subject

I have read the above introduction to this study and have had the opportunity to ask my doctor questions about this study. All my questions have been satisfactorily answered.

I know there may be risks and benefits to participating in this study. I take part in the study on a voluntary basis.

I confirm that I have had enough time to consider this and I know that I can always consult my doctor for more information.

I can withdraw from this study at any time without discrimination or retaliation, and my rights and interests will not be affected.

I also know that if I drop out of the study, especially because of the acupuncture, it would be advantageous for me to report my changes to my doctor and complete the check-related.

If I need to take any other medication as a result of my condition, I will consult my doctor in advance or tell my doctor truthfully afterwards.

I grant access to my research materials to research management, ethics committees or sponsors.

I will receive a signed and dated copy of the informed consent.

In the end, I decide to take part in the study and promise to follow my doctor's advice as much as possible.

Subject's Signature: _____ Date: _____ Tel: _____

If signed by other than subject, indicate relationship:_____

Statement of doctor

I confirm that the patient have been explained in detail about the trial, including her rights and potential benefits and risks, and that I have given her a signed copy of the informed consent.

Doctort's Signature:_____Date:_____Tel: _____